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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/613,105	07/02/2003	Luca Rastelli	Cura 318 Divisional	4239

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EXAMINER	
WOLLENBERGER, LOUIS V	
ART UNIT	PAPER NUMBER
1635	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/09/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/613,105	RASTELLI ET AL.	
	Examiner	Art Unit	
	Louis V. Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,9 and 10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,9 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Exhibit A*.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/29/07 has been entered.

Status of Application/Amendment/Claims

Applicant's response filed 1/29/07 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 8/28/06 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 1/29/07, claims 4-6 and 10–14 are pending. As explained below (Election/Restrictions), Claims 11–14 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Election/Restrictions

Newly submitted claims 11–14 are directed to a related invention that is distinct from the invention originally claimed and examined for the following reasons.

Pursuant to MPEP § 806.05(j), related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants.

In the instant case, new Claims 11–14 are drawn to a method of identifying a cancer cell comprising measuring the expression of a polypeptide, whereas elected claims 4–6 and 10 are drawn to a method of identifying a cancer cell comprising measuring the expression of a nucleic acid. While the inventions are related, they are distinct because the different methods require steps for measuring structurally and functionally distinct molecules. For example, Claims 11–14 embrace method steps for measuring the expression of a protein at the protein level, e.g., using immunoassays (as taught by the specification at page 4). Measuring the expression of a polypeptide requires reagents, skills, and processes unique to the art of protein detection and analysis, whereas the method of claims of 4-6 and 10 is considered to be limited to methods for the detection of nucleic acids such as the gene transcript, or mRNA, corresponding to SEQ ID NO:1, or encoding the protein of SEQ ID NO:2, and would require reagents, skills, and techniques unique to the art of nucleic acid detection. Accordingly, the different methods have a materially different design and do not overlap in scope, and there is nothing of record to show them to be obvious variants. The methods as claimed would differ with regard to the best mode of operation, and would yield different relative information regarding the biological status of the

cell according to whether the indicator of that status is the mRNA or protein level. Furthermore, there is no evidence of record to suggest that the different methods are obvious variants of one another.

Thus, the methods as claimed have different scopes, requiring different keyword searches and considerations of the patent and non-patent literature with regard to novelty, obviousness, written description, and enablement, imposing a burden on the Examiner. Restriction is proper therefor.

Since applicant has received an action on the merits for the originally presented invention, claims 4–6 and 10, drawn to measuring the expression of a nucleic acid, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 11–14 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions or species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C.103(a) of the other invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4–6 and 10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Independent claim 4 recites comparing the expression of the nucleic acid of step (a) in the test sample to expression of a reference nucleic acid encoding an antileukoprotease polypeptide in a normal cell of colon, thyroid or kidney. The term "normal" in Step b of claim 4 is a relative term which renders the claim indefinite. The term "normal" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim Rejections – 35 USC § 102—maintained

Claims 4-6 and 10 remain rejected under 35 U.S.C. 102(e) as being anticipated by Au-Young et al. (US 6,500,938).

Response to Arguments

Applicants argue that Au-Young does not specifically disclose or suggest using the specific subset of nucleic acids which comprise SEQ ID NO: 1 or encode a polypeptide comprising SEQ ID NO:2 to identify the claimed subset of cancer cells (i.e., from colon, thyroid and/or renal cancer).

Applicant's arguments filed 1/29/07 have been fully considered but they are not persuasive.

Au-Young et al. teach methods and materials for making and using microrrays for the measurement and comparison of mRNA expression levels in cells from various tissue types, both cancerous and normal.

At column 4, it is taught that the arrays comprise a plurality of polynucleotide probes specific to distinct genes. More specifically, it is taught that the array may comprise a portion or all of the genes corresponding to SEQ ID Nos: 1-1490, set forth therein in Table 1 beginning at Col. 17-18. Included in this gene set to which microarray capture probes may be designed is nucleic acid sequence SEQ ID NO:1271, which is 100% identical to instantly recited SEQ ID NO:1, as shown by the Office's STIC sequence search (see alignment below).

```
RESULT 1
US-09-016-434-1271
; Sequence 1271, Application US/09016434
; Patent No. 6500938
;  GENERAL INFORMATION:
;    APPLICANT:  Janice Au-Young
;    APPLICANT:  Jeffrey J. Seilhamer
;    TITLE OF INVENTION:  COMPOSITION FOR THE DETECTION OF SIGNALING
;    TITLE OF INVENTION:  PATHWAY GENE EXPRESSION
;    NUMBER OF SEQUENCES:  1490
;
US-09-016-434-1271

  Query Match             100.0%;  Score 594;  DB 3;  Length 594;
  Best Local Similarity   100.0%;  Pred. No. 1.5e-183;
  Matches  594;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 GTCACTCCTGCCTTCACCATGAAGTCCAGCGGCCTCTTCCCCTTCCTGGTGCTGCTTGCC 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 GTCACTCCTGCCTTCACCATGAAGTCCAGCGGCCTCTTCCCCTTCCTGGTGCTGCTTGCC 60

Qy         61 CTGGGAACTCTGGCACCTTGGGCTGTGGAAGGCTCTGGAAAGTCCTTCAAAGCTGGAGTC 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 CTGGGAACTCTGGCACCTTGGGCTGTGGAAGGCTCTGGAAAGTCCTTCAAAGCTGGAGTC 120

Qy        121 TGTCCTCCTAAGAAATCTGCCCAGTGCCTTAGATACAAGAAACCTGAGTGCCAGAGTGAC 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 TGTCCTCCTAAGAAATCTGCCCAGTGCCTTAGATACAAGAAACCTGAGTGCCAGAGTGAC 180

Qy        181 TGGCAGTGTCCAGGGAAGAAGAGATGTTGTCCTGACACTTGTGGCATCAAATGCCTGGAT 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 TGGCAGTGTCCAGGGAAGAAGAGATGTTGTCCTGACACTTGTGGCATCAAATGCCTGGAT 240

Qy        241 CCTGTTGACACCCCAAACCCAACAAGGAGGAAGCCTGGGAAGTGCCCAGTGACTTATGGC 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        241 CCTGTTGACACCCCAAACCCAACAAGGAGGAAGCCTGGGAAGTGCCCAGTGACTTATGGC 300
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Qy       301 CAATGTTTGATGCTTAACCCCCCCAATTTCTGTGAGATGGATGGCCAGTGCAAGCGTGAC 360
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       301 CAATGTTTGATGCTTAACCCCCCCCAATTTCTGTGAGATGGATGGCCAGTGCAAGCGTGAC 360

Qy       361 TTGAAGTGTTGCATGGGCATGTGTGGGAAATCCTGCGTTTCCCCTGTGAAAGCTTGATTC 420
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       361 TTGAAGTGTTGCATGGGCATGTGTGGGAAATCCTGCGTTTCCCCTGTGAAAGCTTGATTC 420

Qy       421 CTGCCATATGGAGGAGGCTCTGGAGTCCTGCTCTGTGTGGTCCAGGTCCTTTCCACCCTG 480
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       421 CTGCCATATGGAGGAGGCTCTGGAGTCCTGCTCTGTGTGGTCCAGGTCCTTTCCACCCTG 480

Qy       481 AGACTTGGCTCCACCACTGATATCCTCCTTTGGGGAAAGGCTTGGCACACAGCAGGCTTT 540
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       481 AGACTTGGCTCCACCACTGATATCCTCCTTTGGGGAAAGGCTTGGCACACAGCAGGCTTT 540

Qy       541 CAAGAAGTGCCAGTTGATCAATGAATAAATAAACGAGCCTATTTCTCTTTGCAC 594
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       541 CAAGAAGTGCCAGTTGATCAATGAATAAATAAACGAGCCTATTTCTCTTTGCAC 594
```

At columns 11-12, it is taught that the microarray can be employed in several applications including diagnostics, that the microarray can be used to monitor the progression of disease, that researchers can assess and catalog the differences in gene expression between healthy and diseased tissues or cells, and that by analyzing changes in patterns of gene expression, disease can be diagnosed at earlier stages before the patient is symptomatic. It is said that the microarray is particularly useful for diagnosing and monitoring the progression of diseases that may be associated with the altered expression of SPPs (signaling pathway polypeptides), which may be associated with certain types of cancer (col. 12, lines 4-20). It is taught that the microarray and expression profiles are particularly useful to diagnose a cancer such as adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma and teratocarcinoma. Such cancers include, but are not limited to, cancers of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid and uterus (underline added).

At column 11, it is taught that microarrays may be used in a method referred to as differential hybridization experiment, wherein target polynucleotides from two or more different biological samples are labeled with two or more different fluorescent labels with different emission wavelengths. Fluorescent signals are detected separately with different photomultipliers set to detect specific wavelengths. The relative abundances/expression levels of the target polynucleotides in two or more samples is obtained. Similarly, at Columns 73 *et seq.* the inventors describe the material compositions of several different matched, normal and diseased tissue RNA libraries from a variety of tissues including colon (COLNTUT02 Library, for example; col. 89 and 90) for array hybridization analysis.

It is clear from the disclosure of Au-Young et al. that side-by-side analysis and the use of internal standards and controls is an integral component of array analysis, and essential for determining the up or down regulation (i.e., increased or decreased expression) of a particular gene in a diseased tissue. It is axiomatic to the nature of this and every other biochemical analysis of a test sample to compare the test or diseased sample to a normal or reference sample, obtained from a patient or source considered to be "normal."

Therefore, Au-Young et al. anticipate the instant invention inasmuch as they teach the instantly claimed method steps for measuring and comparing the expression of SEQ ID NO:1 in kidney, colon, and thyroid cells for cancerous and non-cancerous tissues. SEQ ID NO:1 encodes an antileukoprotease polypeptide (see Table 1, SEQ ID NO:1271, cols. 65-66).

Claim Rejections – 35 USC § 102—withdrawn

The rejection of Claims 1-6, 9, and 10 under 35 U.S.C. 102(e) as being anticipated by Morin et al. (US 2003/0211498) is withdrawn in view of Applicants' amendments to the claims. Morin et al. does not expressly teach measuring the relative expression of instant SEQ ID NO:1 as a diagnostic of thyroid, renal, or colon cancer.

Claim Rejections - 35 USC § 102—maintained

Claims 4–6 remain rejected under 35 U.S.C. 102(e) as being anticipated by Gould-Rothberg et al. (US Patent 6,436,642).

Response to Arguments

Applicants argue that Gould-Rothberg simply teaches that human antileukoprotease was found to be expressed in colorectal cancer and thyroid cancer and upregulated in metastatic thyroid cancer as compared to the non-metastatic thyroid cancer). Applicants argue that Gould-Rothberg does not teach that human antileukoprotease is overexpressed in colon cancer or thyroid cancer as compared to the corresponding normal tissues. There is no teaching or suggestions in Gould-Rothberg to identify a colon or thyroid cancer cell by detecting the overexpression of an antileukoprotease in a test sample as compared to a normal tissue.

Applicant's arguments filed 1/29/07 have been fully considered but they are not persuasive.

As Applicants acknowledge, Gould-Rothberg et al. teach that antileukoprotease is expressed in lung, breast, oropharyngeal, bladder, endometrial, ovarian, and colorectal carcinomas and is up-regulated in metastatic vs. non-metastatic thyroid cancer (col. 15 bridging to 16; col. 2, lines 5-25). The term "up-regulated" is considered to be synonomous with increased

expression or over-expression. Gould-Rothberg et al. clearly teach that antileukoprotease is differentially expressed, and more specifically over expressed in metastic thyroid cancer, and therefore thyroid cancer.

It is also clear that Gould-Rothberg et al.'s disclosure teaches that measuring antileukoprotease expression levels, as well as other genes, in a sample cell population allows for the type and tumor stage of the cells in the sample to be determined. For example, at column 3, it is stated that "...the measurement of the expression profiles of one or more of these sequences can be used, for example, to diagnose a neoplasm, to categorize a neoplasm, to assess prognosis, and to monitor the efficacy of neoplasm treatment." See also cols. 31 *et seq.*

Gould-Rothberg et al. expressly teach measuring and comparing levels antileukoprotease (GenBank Accession No. X04470) in test samples to those of normal samples using methods well known in the art to identify thyroid cancer cells (See col. 26 *et seq.*; see also column 15, line 63, to column 16, line 10; and column 2, lines 5-25).

The instant claimed methods embrace methods for identifying metastatic and non-metastatic thyroid cancer cells from any tissue in any animal by measuring the expression of an antileukoprotease sequence corresponding to SEQ ID NO:1.

Gould-Rothberg et al. also state that "Other aspects, advantages, and modifications are within the scope of the following claims. For example, the neoplasm described herein can be a thyroid carcinoma, a breast carcinoma, a colorectal carcinoma, and/or an ovarian carcinoma. Similarly, the methods described herein can also be used for metastatic neoplasms from non-thyroid tumors, e.g., carcinomas such as ovarian, breast, and colorectal carcinomas."

Gould-Rothberg et al. teaches and therefore anticipates the instant method for diagnosing and identifying thyroid and colorectal cancers comprising the steps of measuring and comparing the relative expression of antileukoprotease in normal and diseased tissues, whereby and increase in the relative expression is indicative or metastatic thyroid cancer, as well as other cancers such as colorectal cancer.

Claim Rejections - 35 USC § 103—new

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 4–6 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Garver et al. (1994) *Gene Therapy* 1:46-50; Morita et al. (1999) *Advances Enzyme Regul.* 39:341-355; Alkemade et al. (1993) *Am. J. Pathol.* 143:1679-1687: Heinzel et al. (1986) *Eur. J. Biochem.* 160:61-67; and Willey et al. (1998) *Am. J. Respir. Cell Mol.* 19:6-17.

The prior art taught a correlation between secretory leukocyte protease inhibitor (*SLPI*) expression levels and tumor progression. For example, Garver et al. taught that SLP1 is widely expressed in different carcinomas, including lung, breast, ovarian, and colorectal carcinomas. Garver et al. taught that, based on their studies, it seems probable that other carcinomas such as prostate and oesophageal will be found to express SLP1 as well. Garver et al. state that based on its widespread expression, SLP1 may represent a therapeutic target to selectively kill SLP1-expressing malignant cells (page 49). Accordingly, Garver et al. taught that antileukoprotease expression is a marker and potential therapeutic target associated with cancer cell proliferation in many different tissues.

Garver et al. do not expressly teach that SLP1 is overexpressed in thyroid, renal, or colon cancers, or that the identification of such cancers may be determined exclusively on the basis of overexpression of SLP1 relative to normal tissue.

However, Morita et al. taught that the mouse ortholog of human secretory leukocyte protease inhibitor, or mSLPI, is overexpressed in a murine leukemias and liver metastatic tumor

cells (Fig. 1, for example). Morita et al. expressly compare the mouse and human orthologs, stating that, on the basis of their results, it would be interesting to determine whether or not an isoform of human SLPI mRNA is present in human leukemias or metastatic tumors (page 352).

Alkemade et al. taught that a skin-derived antileukoproteinase (SKALP) is differentially expressed in basal and squamous cell carcinoma, as well as other hyperproliferative conditions. It is suggested that SKALP/elafin is a marker for abnormal or disturbed squamous differentiation. A possible role of SKALP/elafin in the control of tumor cell invasion is discussed.

Heinzel et al. taught the cDNA sequence of human antileukoprotease, enabling one of skill in the art to design probes and primers for the detection and quantification of human antileukoproteinase in cells and tissues via art-recognized methods such as Northern blotting, in situ hybridization, and quantitative PCR. The sequence was published as GenBank Accession No. X04470, on or about Apr 21, 1993, according to the NCBI website (Exhibit A, attached).

The instant application discloses that instantly recited SEQ ID NO:1 (claims 1 and 4) is identical to GenBank Accession No. X04470 (see page 2 of 60/207104 and page 18 of the instant application).

Willey et al. taught a method for quantitative PCR for measuring the relative differences in expression of virtually any gene in any cell from any tissue.

Accordingly, it would have been obvious at the time the instant invention was made to measure and quantify the relative expression of human antileukoproteinase in thyroid, colon, or renal cells, obtained from cultures in vitro or tissues in vivo, as a marker for the presence of cancer cells therein. Given that the prior art taught that the antileukoproteinase is expressed in many types of cancers in humans, and overexpressed in certain cancers in mice, and that it may

play a role in tumor cell invasion, it would have been obvious to associate increased expression with the presence of cancer cells therein.

One of skill would have been well motivated and have had a reasonable expectation of success given that the combination of cited prior art references as a whole taught and/or suggested that antileukoproteinase is abnormally expressed in human and mouse cancers, and given that the prior art taught both the cDNA sequence of human antileukoproteinase and methods for rapid, accurate, PCR-based semi-quantitative assessment of gene expression in tissues and cells.

Accordingly, in the absent of convincing evidence to the contrary, the instantly claimed invention would have been *prima facie* obvious to one of skill in the art at the time the invention was made.

Response to Applicants' Arguments

Applicants' arguments presented on 1/29/07 not specifically addressed above are considered to be moot in view of Applicants' amendments to the claims and in view of the new and/or reiterated rejections stated herein, above.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis V. Wollenberger whose telephone number is 571-272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on (571)272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LVW
Examiner Art Unit 1635
March 26, 2007

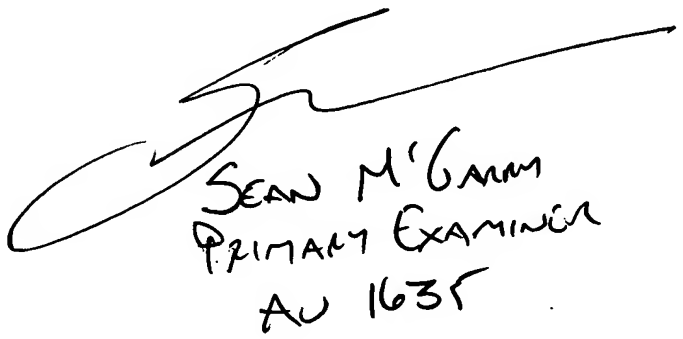

Exhibit A

NCBI

Sequence Revision History

Revision history for X04470

GI	Version	Update Date	Status	I	II
28638	1	Oct 6 2006 3:42 PM	Live	◉	○
28638	1	Apr 19 2005 2:05 AM	Dead	○	◉
28638	1	Sep 9 2004 11:25 PM	Dead	○	○
28638	1	Aug 4 2003 7:32 PM	Dead	○	○
28638	1	Oct 13 2002 4:59 PM	Dead	○	○
28638	1	Mar 9 1999 1:12 AM	Dead	○	○
28638	1	May 30 1996 11:39 PM	Dead	○	○
28638	1	Mar 27 1995 12:46 AM	Dead	○	○
28638	1	Nov 30 1994 5:19 PM	Dead	○	○
28638	1	Sep 1 1993 3:49 AM	Dead	○	○
28638	1	Apr 21 1993 3:20 AM	Dead	○	○

Accession X04470 was first seen at NCBI on Apr 21 1993 3:20 AM